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Title: NEW PHARMACEUTICAL COMPOSITION  
WITH ANAESTHETIC EFFECT

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## NEW PHARMACEUTICAL COMPOSITION WITH ANAESTHETIC EFFECT

*Shwa 371 of PCT/SE97/00566 filed 4/1/97*The field of the invention

- 5 The present invention is directed to a new pharmaceutical composition and its use in therapy, particularly as an anaesthetic for use on mucous membranes and particularly within the oral cavity.

10 Background and prior art

- It is estimated that approximately 10-13 % of the population suffers from periodontal diseases with pathological periodontal pockets. In order to eliminate or control the disease and arrest further periodontal tissue destruction, periodontal pockets need repeated
- 15 subgingival mechanical debridement/cleansing. The number of periodontal pockets in a patient may vary as can the pocket depth measurement. Approximately 40 % of all periodontal scaling procedures performed involve some kind of anaesthesia.

- Accumulation of bacterial plaque on teeth and in the gingival sulcus elicits an inflammatory
- 20 response in the marginal gingiva which may spread in an apical direction and result in loss of tooth support with the formation of periodontal pockets. The object of mechanical debridement of periodontal pockets is to control and arrest further destruction of tooth support by removal of plaque and calculus from within the pockets.

- 25 The majority of the scaling procedures are performed by hygienists. The main use of anaesthesia techniques used in conjunction with periodontal scaling is either a nerve block or infiltration. Infiltration anaesthesia is either carried out alone or in combination with topical anaesthesia, mainly jelly, ointment or spray. However, the problem with existing topical products are lack of efficacy due to inadequate depth of penetration, too short
- 30 duration and difficulties in administration due to spread, taste etc.

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Thus, the problem underlying the present invention is to provide a pharmaceutical composition which would provide effective pain relief in conjunction with periodontal scaling and root planing following local administration. In other words, the object of the invention is to provide a local anaesthetic that can be applied in a facile manner in the oral cavity, and more precisely within periodontal pockets. A further object of the invention is to provide a pharmaceutical composition having a short onset time and an adequate duration for the intended procedure, with no inconvenient anaesthesia.

Outline of the invention

The problem identified above has now been solved by providing a new pharmaceutical composition which preferably is in form of an emulsion, more preferably in form of a microemulsion, comprising the following ingredients:

(i) One or more local anaesthetics in oil form in the final composition;

(ii) one or more surfactants, together present in an amount effective to produce a homogenous formulation; and

(iii) water up to 100 % by weight, based on the total weight of the composition.

The local anaesthetic in the final composition is one or more local anaesthetics in oil form as such, or a eutectic mixture formed by two or more local anaesthetics. The amount of the local anaesthetic in the oil phase depends on the pH-value of the formulation.

In a particularly preferred embodiment of the invention the local anaesthetic is a eutectic mixture of lidocaine base and prilocaine base.

In a further embodiment of the invention a eutectic mixture may also be formed by two or more substances, where at least one of these substances is a local anaesthetic.

The amount of the local anaesthetic or mixture of local anaesthetics is preferably in the range 0.5 - 20 % by weight, more preferably in the range 2-7 % by weight, based on the total weight of the composition.

The local anaesthetic(s) in the final composition are present in a non-solid form.

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By the wording "surfactant" we mean any agent that acts as a solubilizer and/or as an emulsifier and/or as a thickening agent with thermoreversible gelling properties. The wording surfactant is also intended to include thickening agents without thermoreversible properties. If only one surfactant is used in the composition, it must be selected with care and in suitable amounts so that it acts both as a solubilizer and/or as an emulsifier, as well as a thickening agent with thermoreversible gelling properties. If more than one surfactant is present in the composition, at least one of the surfactants should have thermoreversible gelling properties. The total amount of the surfactant(s) should be present in an amount effective to produce a homogenous formulation.

The surfactants are preferably selected from non-ionic surfactants, more preferably from any non-ionic poloxamer known in the art.

Poloxamers are synthetic block copolymers of hydrophilic ethylene oxide chains and hydrophobic propylene oxide chains, having the general formula  $\text{HO} \cdot [\text{C}_2\text{H}_4\text{O}]_a \cdot [\text{C}_3\text{H}_6\text{O}]_b \cdot [\text{C}_2\text{H}_4\text{O}]_a \cdot \text{H}$ , a and b representing the number of the hydrophilic and hydrophobic chains respectively.

By choosing the surfactant(s) having hydrophobic and hydrophilic domains in appropriate amounts, in combination with an appropriate amount of the local anaesthetic or mixture of local anaesthetics, it is possible to achieve a composition having suitable thermoreversible gelling properties, i.e. the system remains less viscous at room temperature, and upon application into a periodontal pocket the viscosity of the composition is increased. In other words, the pharmaceutical composition according to the present invention is less viscous at room temperature. Above this temperature the composition is more viscous, providing the advantage of remaining in the periodontal pockets for the time necessary to induce local anaesthesia. The change in viscosity is reversible with temperature.

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In a particularly preferred embodiment of the invention the surfactant is one or more of Lutrol F68<sup>®</sup>, which also has the name poloxamer 188 and wherein a= 80 and b=27, and Lutrol F127<sup>®</sup>, which also has the name poloxamer 407 and wherein a=101 and b=56, the  
5 definitions being in accordance with USP (1995) NF18, p. 2279. Lutrol F68<sup>®</sup> and Lutrol F127<sup>®</sup> are commercially available from BASF.

In a further preferred embodiment of the invention the surfactant Arlatone 289<sup>®</sup> is used, which also has the name polyoxyethylene hydrogenated castor oil, as well as Adinol CT95<sup>®</sup>  
10 which is sodium N-methyl N-cocoyl taurate.

The total amount of surfactant(s) is preferably present in an amount of up to 50 % by weight, based on the total weight of the composition.

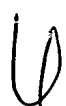
15 The pH-value of the pharmaceutical composition is adjusted with suitable acid or base in such a way that the final pH-value for the composition is:

(A)  $\text{pH} \geq [\text{pK}_a (\text{local anaesthetic}) - 1.0]$  if the composition comprises one local anaesthetic;  
or

20 (B)  $\text{pH} \geq [\text{pK}_a (\text{local anaesthetic with the lowest pK}_a \text{ value}) - 1.0]$  if the composition comprises two or more local anaesthetics.

Preferably the pH is over 7.5.

25 Since local anaesthetics by nature have an unpleasant bitter taste, one or more taste masking agents may optionally be added to the pharmaceutical composition. The choice of taste masking agents will be appreciated by a person skilled in the art, but as an example any fruit flavours may be mentioned.



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For the definition of emulsions, we refer to *Pharmaceutics, The Science of Dosage Form Design*, 1988, p. 109-110, by ME Aulton.

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In the final composition a fraction of the local anaesthetic or mixture of local anaesthetics are present in oil form. The size of this fraction, local anaesthetics in oil form, depends on the pH of the composition.

- 5 The best mode of performing the invention known at present, is to use the composition according to Example 1.

#### Methods of preparation

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The pharmaceutical composition according to the present invention may be prepared by the following steps:

- (i) the local anaesthetic(s) and the surfactant with the lowest molecular weight if more than  
15 one surfactant is used, are melted together;
- (ii) a part of the water is slowly added to the melt (i) during homogenization, forming an emulsion concentrate;
- 20 (iii) if more than one surfactant is used, the surfactant with the higher molecular weight is dispersed in water;
- (iv) the emulsion concentrate of step (ii) and part of the surfactant solution of step (iii) are thoroughly mixed;
- 25 (v) the pH-value is adjusted by the addition of a suitable acid or base;
- (vi) the weight is adjusted with water to the final weight of the composition.
- 30 The composition is preferably kept at 5 °C until a homogenous composition is obtained.



Detailed description of the invention

The invention will now be described in more detail by the following examples, which are not to be construed as limiting the invention.

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Example 1                      [% by weight]

Lidocaine                      2.50

Prilocaine                      2.50

10    Lutrol F68<sup>®</sup>                      5.50Lutrol F127<sup>®</sup>                      15.50

purified water up to a total weight of 100 %.

15    The composition was prepared by following the procedure described above, and the pH-value was adjusted by adding 2 M hydrochloric acid.

Example 2                      [% by weight]

Lidocaine                      2.50

Prilocaine                      2.50

20    Lutrol F68<sup>®</sup>                      5.00Lutrol F127<sup>®</sup>                      16.25

purified water up to a total weight of 100 %.

25    The composition was prepared by following the procedure described above, and the pH-value was adjusted by adding 2 M hydrochloric acid.

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	<u>Example 3</u>	<u>[% by weight]</u>
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	Lidocaine	2.25
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	Prilocaine	2.25
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5	Lutrol F68 <sup>®</sup>	3.5
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	Lutrol F127 <sup>®</sup>	14.0
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purified water up to a total weight of 100 %.

10 The composition was prepared by following the procedure described above, and the pH-value was adjusted by adding 2 M hydrochloric acid.

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	<u>Example 4</u>	<u>[% by weight]</u>
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	Lidocaine	2.25
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	Prilocaine	2.25
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15	Arlatone 289 <sup>®</sup>	1.90
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	Adinol CT95 <sup>®</sup>	0.07
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	Lutrol F127	14.00
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purified water up to a total weight of 100 %.

20 The composition was prepared by following the procedure described above, and the pH-value was adjusted by adding 2 M hydrochloric acid.

THIX

Example 5                      [% by weight]

Lidocaine                      2.25

Prilocaine                    2.25

5    Arlatone 289<sup>®</sup>              1.90

Adinol CT95<sup>®</sup>                0.16

Lutrol F127                  14.00

purified water up to a total weight of 100 %.

10    The composition was prepared by following the procedure described above, and the pH-value was adjusted by adding 2 M hydrochloric acid.

THIX

Example 6                      [% by weight]

15    Lidocaine                      2.25

Prilocaine                    2.25

Arlatone 289<sup>®</sup>                1.90

Adinol CT95<sup>®</sup>                0.28

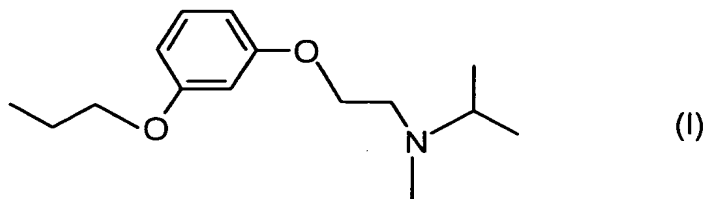
Lutrol F127                  14.00

20    purified water up to a total weight of 100 %.

The composition was prepared by following the procedure described above, and the pH-value was adjusted by adding 2 M hydrochloric acid.

Example 7 and 8

In Examples 7 and 8, a local anaesthetic of the formula (I) was used as the active ingredient.



This compound is disclosed in the International Patent Application ~~SE96/01361~~ <sup>PCT/SE96/01361</sup>.

The following pharmaceutical compositions were prepared.

Example 7 [% by weight]

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Compound (I)	2.5
Lutrol F127 <sup>®</sup>	17.0
Lutrol F68 <sup>®</sup>	5.5

purified water up to a total weight of 100 %.

The composition was prepared by following the procedure described above, and the pH-value was adjusted by adding 2 M hydrochloric acid.

Example 8 [% by weight]

Handwritten: T122X

Compound (I)	2.5
Lutrol F127 <sup>®</sup>	20.0
Lutrol F68 <sup>®</sup>	5.5

purified water up to a total weight of 100 %.

The composition was prepared by following the procedure described above, and the pH-value was adjusted by adding 2 M hydrochloric acid.

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### Biological studies

10 A pharmaceutical composition according to Example 1 was applied to a human periodontal pocket with a blunt end needle. After an onset time of 30 - 45 seconds, a satisfactory anaesthetic effect had been achieved in order that periodontal scaling could be performed. The scaling was initiated, and the time taken to scale the tooth was noted. At the end of the scaling, the intensity of pain was measured by means of a visual analogue scale (VAS). The duration of the anaesthetic effect was 10-20 minutes.

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